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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 11-23-1999

SUBJECT: PP#9F5045. Difenconazole (Helix™) in or on Canola.
HED Risk Assessment. DP Barcode: D258774. PC Code: 128847.
Submission #: S552610. Case #: 290691.

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and exposure models and conduct dietary, occupational, residential and aggregate risk assessments, as needed, to estimate the risk to human health that will result from the use of difenconazole in/on canola.

A summary of the findings and an assessment of human risk resulting from the proposed use of difenconazole is provided in this document. The hazard assessment was provided by Albin Kocialski of Registration Action Branch 1 (RAB1), the residue chemistry data review and dietary risk assessment by Susie Chun of RAB1, and occupational/residential assessment by Dana Vogel of RAB1.

Recommendation for Tolerances

Provided a revised Section F is submitted, the residue chemistry and toxicological data bases support the establishment of the following proposed tolerance for residues of difenoconazole expressed as parent only:

Canola, seed – 0.1 ppm

Registration should be made conditional upon completion of the following:

- The petition method validation (PMV) of the proposed analytical enforcement method.

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1.0 EXECUTIVE SUMMARY

HED has conducted a risk assessment for difenoconazole ([[(2S,4R)/(2R,4S)]/[(2R,4R)/(2S,4S)]1-{2-[4-(4-chlorophenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1*H*-1,2,4-triazole) in support of the establishment of a permanent tolerance on canola. The tolerance on canola is a new use. HED has evaluated toxicology and residue data for difenoconazole submitted by Novartis Corporation. **A petition method validation (PMV) has been requested but has not been completed for the proposed enforcement method; a revised Section F is also required. Therefore, the data are adequate to support a conditional Section 3 registration and the establishment of permanent tolerances in/on canola, seed, provided a revised Section F is submitted.**

Difenoconazole is a systemic fungicide and is effective for the control of several seed and soil-born fungi. It can be used foliarly or as a seed treatment. For the purposes of this action, a liquid ready-to-use formulation (Helix™) is being proposed and is intended as a seed treatment. Helix™ is a multi-active ingredient formulation. Besides difenoconazole, it is comprised of thiamethoxam (insecticide), (R)-[(2,6-dimethylphenyl)-methoxyacetyl-amino]-propionic acid methyl ester (fungicide), and fludioxonil (fungicide). Fludioxonil (40 § CFR 180.516) and (R)-[(2,6-dimethylphenyl)-methoxyacetyl-amino]-propionic acid methyl ester (40 CFR § 180.408, used in place of metalaxyl (Memo, D223261, L. Kutney, 4/24/96)) are registered for use on canola. The thiamethoxam use in/on canola will be addressed in a separate document.

Helix™ is applied using standard slurry seed treatment equipment. The maximum application rate is 23 fl. oz./100 lbs. of seed or 0.025 lbs. ai/100 lbs. of seed.

There are no proposed or existing residential uses for difenoconazole. Therefore, the aggregate exposure is limited to dietary exposure from food and water only.

Hazard Assessment

The overall quality of the toxicology database is good. Confidence in the hazard and dose response is also good. There are no toxicology data gaps. The toxicological database for difenoconazole is adequate to support a Section 3 registration and permanent tolerance.

On September 8, 1998, the HED's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of difenoconazole, reconfirmed the Reference Dose (RfD), addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996, and selected the toxicological endpoints for acute and chronic dietary as well as occupational exposure risk assessments (there are no residential uses at this time for difenoconazole). The FQPA Safety Factor Committee (SFC) met on October 19, 1998 and addressed the potential enhanced sensitivity to infants and children as required by FQPA and recommended for reduction of the 10x FQPA Safety Factor (SF) to 1x.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not considered to be an eye or skin irritant and is not a sensitizer. It is not neurotoxic or mutagenic. It is not a developmental or reproductive toxicant. Chronic effects in the rat study are seen as cumulative decreases in body weight gains. Evidence for carcinogenicity was seen in only one species, mice, where liver tumors were induced at doses

which were considered to be excessively high for carcinogenicity testing. No evidence of carcinogenicity was seen in rats.

The HED Cancer Peer Review Committee (CPRC) met on May 18, 1994 to discuss and evaluate the weight of the evidence for the carcinogenic potential of difenoconazole. The CPRC concluded that difenoconazole should be classified as a Group C - **possible human carcinogen** and recommended, for the purpose of risk assessment, that the margin-of-exposure (MOE) approach should be used for the quantification of human risk (Memo, Jess Rowland and Esther Rinde, 7/27/94). The decision to classify difenoconazole as a Group C carcinogen was based on statistically significant increases in liver adenomas, carcinomas, and combined adenomas and carcinomas in both sexes of CD-1 mice, only at doses that were considered to be excessively high for carcinogenicity testing. The MOE approach was recommended because there was only very weak (limited) evidence of carcinogenic potential at dose levels not considered to be excessive, with significant changes observed only at excessive doses. In addition there was no evidence of genotoxicity.

Dose Response Assessment

An acute reference dose (aRfD) of 0.25 mg/kg was established for the subpopulation group, females 13+ years old only, based on a no-observed-adverse-effect level (NOAEL) of 25 mg/kg from a developmental study in the rabbit. Effects seen at the next higher dose level of 75 mg/kg were increases in post-implantation loss and resorptions per doe and a significant decrease in fetal body weight. These effects are presumed to occur after a single exposure *in utero* and, therefore, are considered to be appropriate for this risk assessment.

An acute dose and endpoint were not selected for the general population group (including infants and children) because there were no effects observed in oral toxicology studies, including maternal toxicity in the developmental toxicity studies in rats and rabbits, that are attributable to a single exposure [dose].

The chronic reference dose (cRfD) of 0.01 mg/kg/day was determined on the basis of a two year chronic feeding oncogenicity study in the rat. The NOAEL of 0.96 mg/kg/day (equal to 1.0 mg/kg/day) was based on cumulative decreases in body weight gains at the lowest-observed-adverse-effect level (LOAEL) of 24.12 mg/kg/day. This cRfD was originally established at an RfD meeting in 1994 and was re-confirmed by the HIARC on September 8, 1998 (Memo, A. Kocialski and Jess Rowland 9/25/98).

The FQPA SFC recommended that the 10x FQPA SF be reduced to a 1x factor since the toxicology data base is complete, and there is no indication of increased susceptibility of rats or rabbits to *in utero* and/or post-natal exposure to difenoconazole based on results from the developmental and the reproductive toxicity studies (Memo, B. Tarplee, 10/28/98).

Since the FQPA SF was removed (i.e., reduced to 1x), the aRfD and cRfD are equivalent to the aPAD and cPAD, respectively.

At this time, HED has not defined the level of concern for cancer risk using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the Q_1^* approach. The Q_1^* was determined to be $0.157 \text{ (mg/kg/day)}^{-1}$. This value incorporates the $\frac{3}{4}$ scaling factor and is based

on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunzman, 12/8/98).

A short-term dermal dose/endpoint was chosen from a developmental rabbit study. The HIARC selected an oral NOAEL of 25 mg/kg/day based on post-implantation loss, increased resorptions per dose, and decreased body weight seen at 75 mg/kg/day (LOAEL). An intermediate-term dermal endpoint was chosen from a two-generation reproduction rat study. The HIARC selected an oral NOAEL of 1.25 mg/kg/day based on decreased pup weight on day 21 at 12.5 mg/kg/day (LOAEL). A long-term dermal endpoint was not identified by HIARC because long-term dermal exposure is not expected based on a one time application as a seed treatment.

An inhalation dose/endpoint was not identified by HIARC because there is minimal concern for potential inhalation exposure/risk based on the low acute toxicity (Toxicity Category IV), the application rate, the application method, and the number of applications [1x].

Occupational and Residential Risk Estimates

This occupational exposure assessment addresses the use of Helix™ (EPA reg. # 100-0GL), insecticide/fungicide combination product, which contains 1.25% of difenoconazole. Difenoconazole is a fungicide used as a systemic seed dressing to control certain seed-borne and soil-borne diseases. The product label specifies a maximum application rate of 0.025 pounds of difenoconazole per 100 pounds of seed.

Based on the proposed canola seed treatment uses of difenoconazole, the potential for occupational exposures exists. There are no residential uses. For this action, occupational exposure to difenoconazole is limited to the workers involved in the commercial seed treatment and planting of treated canola seeds. The label specifies that this product is only for use in commercial seed treatment plants. In the agricultural setting, canola planting usually consists of the following functions; mixer/loader and driver/planter. The highest exposure will be for the mixer/loader scenario which involves opening the treated seed bags and emptying the contents into the application equipment. Exposure and risk for the planter/driver is not expected to exceed that of the mixer/loader. Therefore, exposure calculations were done for the mixer/loader scenario only. All risk estimates for the mixer/loader scenario are well below the Agency's level of concern.

The HIARC determined that inhalation risk assessments are not required since toxicological concerns were not identified for this route of exposure. Only short- and intermediate-term dermal exposure is expected for the canola use due to the limited number of applications per year. Long-term exposure is not expected for use of difenoconazole on agricultural or non-agricultural areas due to one-time application. Exposures from post-application residues of difenoconazole are not expected to pose any risks.

The cancer risk endpoint established for the active ingredient is a Q_1^* of 0.157 mg/kg/day (Memo, Lori Brunzman, 12/8/98). Using the Q_1^* approach, occupational cancer risk for commercial seed treaters and farm workers does not exceed HED's level of concern. The calculated cancer risk is not expected to exceed 8.5×10^{-5} and 8.6×10^{-8} for the seed treaters and farm workers, respectively.

Dietary Exposure Estimate

The following three dietary exposure risk assessments were conducted for the existing uses and proposed new use on canola: acute (for females 13-50 years old only), chronic (non-cancer, for the U.S. population and all subgroups) and chronic (cancer, for the general U.S. population only). An acute dietary analysis was not performed for the general U.S. population or children and infant subgroups as no doses or endpoints were selected. The acute dietary analysis is a conservative Tier I estimate with the use of tolerance level residues and 100% crop treated (CT). The chronic (non-cancer and cancer) dietary analyses were refined estimates using anticipated residues (ARs) from field trial data and % CT information provided by the Biological and Economics Analysis Division (BEAD) (dated 2/9/99, 12/17/98). No monitoring data from USDA's Pesticide Data Program (PDP) or FDA's Surveillance Monitoring Program were available for difenoconazole.

Acute Dietary

For acute dietary exposure risk, HED's level of concern is >100% aPAD. Exposures at the 95th percentile for all the females 13-50 years old subgroups was <1% aPAD. Therefore, the acute dietary risk associated with the proposed use of difenoconazole on canola is below HED's level of concern.

Chronic (non-cancer) Dietary

For chronic (non-cancer) dietary exposure risk, HED's level of concern is >100% cPAD. All chronic (non-cancer) % cPADs for all subgroups were <1%. Therefore, the results of the chronic dietary exposure analysis indicate that the chronic (non-cancer) dietary risk associated with the proposed use of difenoconazole is below HED's level of concern.

Chronic (cancer) Dietary

HED generally considers 1×10^{-6} as negligible risk (i.e., less than 1 in 1 million) for cancer. The results of this analysis indicate that the cancer dietary risk of 8.6×10^{-7} associated with the proposed use of difenoconazole is below HED's level of concern.

Drinking Water Exposure

Tier I estimated environmental concentrations (EECs) were provided for both surface water (GENEEC model) and ground water (SCI-GROW) by the Environmental Fate and Effects Division (EFED) (Memo, J. Hetrick, 2/9/99). The estimated average concentration of difenoconazole in ground water is **0.00084 ppb** (to be used for acute and chronic risk assessments). The estimated maximum concentrations of difenoconazole in surface water are **0.125 ppb** and **0.048 ppb**, (to be used for acute and chronic risk assessments, respectively). According to OPP drinking water guidance (HED SOP 99.5), the 56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment would be **0.016 ppb**. Tier I models represent the most conservative estimates of potential residues in drinking water. The drinking water assessment for difenoconazole is tentative because there are insufficient data to complete a quantitative environmental fate and transport assessment using Tier 1 FQPA models. Since

difenoconazole is used solely as a fungicide on the seed coat of small grains to control soil-borne fungi, it is not expected to pose a major threat to ground and surface waters. These modeling assumptions are expected to yield conservative estimates for difenoconazole concentrations in drinking water. DWLOCs for acute, chronic (non-cancer), and cancer dietary risk from drinking water were calculated.

The DWLOCs for difenoconazole in surface and ground water are: from acute exposure for females (13+ years old/nursing) - **7470 ppb**; from chronic (non-cancer) exposure for the U.S. population - **350 ppb**; females (13+ years old/nursing) - **300 ppb**; non-nursing infants (<1 year old) - **100 ppb**; and from chronic (cancer) exposure for the U.S. population - **0.048 ppb**.

Aggregate Risk Estimate

Because there are no uses of difenoconazole that could result in residential exposures, this aggregate risk assessment takes into consideration dietary food and water exposure.

Acute and chronic (non-cancer and cancer) aggregate exposure and risk estimates do not exceed HED's level of concern. For acute aggregate risk assessment, HED has no concern for acute effects through exposure to difenoconazole in drinking water. The acute DWLOC is greater than the surface and ground water EECs. Chronic (non-cancer) aggregate exposure and risk estimates do not exceed HED's level of concern. For chronic (non-cancer) risk assessment, HED has no concern for chronic (non-cancer) effects through exposure to difenoconazole in drinking water. The chronic DWLOCs are greater than the surface and ground water EEC. Chronic (cancer) aggregate exposure and risk estimates exceed HED's level of concern. For cancer risk assessment, HED has no concerns for chronic (cancer) effects through exposure to difenoconazole in drinking water via surface or ground water. Both the ground and surface water EECs were less than the cancer DWLOC. Therefore, HED concludes with reasonable certainty that residues of difenoconazole in drinking water do not contribute significantly to the acute or chronic (non-cancer and cancer) aggregate human health risk at the present time.

Recommendation for Tolerances

Adequate residue chemistry and toxicology data have been submitted to support the establishment of the following permanent tolerance for residues of difenoconazole expressed as parent only:

Canola, seed 0.01 ppm

However, the residue chemistry data support a conditional registration provided that a revised Section F is submitted. The registration should remain conditional until a successful PMV of the proposed analytical enforcement method is completed.

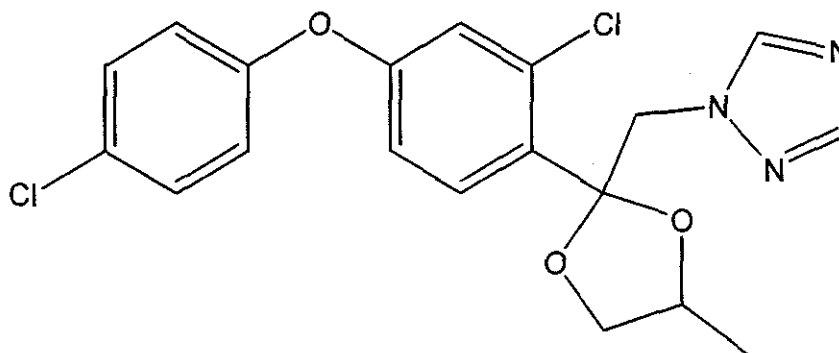
To provide for the re-evaluation of the ARs, the Agency will require under Section 408(b)(2)(E) that additional residue data be submitted within five years.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1. Identification of Active Ingredients

Chemical Name:	([(2S,4R)/(2R,4S)]/[(2R,4R)/(2S,4S)]1-{2-[4-(4-chloro phenoxy)-2-chlorophenyl]-4-methyl-1,3-dioxolan-2-yl-methyl}-1 <i>H</i> -1,2,4-triazole)	
Common Name:	Difenoconazole	
PC Code Number:	128847	
CAS Registry No.:	119446-68-3	
Empirical Formula:	C ₁₉ H ₁₇ Cl ₂ N ₃ O ₃	
Molecular Weight:	405.06	
Vapor Pressure (PAI):	2.5 x 10 ⁻¹⁰ mm Hg @ 25°C	
Solubility: (g/100 mL , @ 25°C)	water	3.3 ppm @ 20°C
	1-octanol	25
	acetone	88
	ethanol	89
	toluene	77
	n-hexane	0.5
Octanol/Water Partition Coefficient:	log K _{ow} =	4.2 @ 25°C
Dissociation Constant:	pK _a < 0	

2.2. Structural Formula (Difenoconazole)



2.3. Physical and Chemical Properties

Product chemistry data for the difenoconazole technical product were reviewed (Memo, D172067, R. Lascola, 10/26/92; Memo, G. Kramer, D194842, 3/30/94; Memo, G. Kramer, D203644, 6/16/94; Memo, G. Kramer, D210080, 1/19/95) and deemed adequate to fulfill the requirements for a permanent tolerance request. No additional product chemistry data are required.

3.0 HAZARD CHARACTERIZATION

3.1. Hazard Profile

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is considered to be a mild eye irritant and a slight skin irritant and is not a dermal skin sensitizer.

Subchronic studies in mice and rats manifested decreased body weights, decreased body weight gains and effects on the liver at 200 ppm and higher. Microscopic examination of the eyes of dogs at 3000 ppm revealed unilateral and bilateral lenticular cataracts in both sexes of animals. Decreased body weights, body weight gains, and food consumption were reported in a 21 day rabbit dermal study at the LOAEL of 100 mg/kg/day.

Chronic studies in rats revealed decreased body weight gains and increased liver weights along with hepatocellular hypertrophy. Clinical chemistry data supported the liver pathology data suggesting that the liver was the primary target organ. There were no treatment related neoplastic effects. The LOAEL was 500 ppm (equal to 24.12 and 32.79 mg/kg/day for males and females respectively) and the NOAEL was 20 ppm (equal to 0.96 and 1.27 mg/kg/day for males and females respectively).

Chronic feeding studies in mice showed decreased body weight gains in male and female mice at termination. Treatment related non-neoplastic lesions were confined to the liver and were supported by the clinical chemistry data at a level of 300 ppm (46.29 and 57.79 mg/kg/day for males and females respectively). Liver tumors were observed in mice at 300 ppm and higher; however, based on the excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at the two lower doses of 10 and 30 ppm and the absence of genotoxic effects, the Cancer Peer Review Committee (CPRC) (Memo, Jess Rowland and Esther Rinde, 7/27/94) recommended for a cancer classification of C (**possible human carcinogen**) and advocated a MOE approach in risk assessment utilizing the NOAEL of 30 ppm (4.7 and 5.6 mg/kg/day in males and females respectively) and the LOAEL of 300 ppm (46.3 and 57.8 mg/kg/day in males and females respectively) from the mouse study using only those biological endpoints which were related to tumor development (i.e. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). However, at this time, the Agency has not defined the level of concern for cancer using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the Q_1^* approach. The Q_1^* was determined to be 1.57×10^{-1} (mg/kg/day)⁻¹. This value incorporates the 3/4 scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunsman, 12/8/98).

The chronic study in beagle dogs revealed decreased body weight gains throughout the study at 500 ppm and increased levels of alkaline phosphatase at 1500 ppm (equal to 51.2 and 44.3 mg/kg/day for males and females respectively). The LOAEL was **500 ppm** (equal to **16.4** and **19.4** mg/kg/day for males and females respectively) and the NOAEL was **100 ppm** (equal to **3.4** and **3.7** mg/kg/day for males and females respectively).

The results of the 2-generation reproduction and developmental studies did not demonstrate increased sensitivity to infants and children.

Neurotoxicity studies are not applicable as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that difenoconazole possesses neurotoxic properties. It is not structurally related to known neurotoxic compounds.

Mutagenicity studies indicated that difenoconazole was not mutagenic under the test conditions.

Metabolism studies in rats indicated that peak absorption occurred between 28 and 48 hours post-dosing. Elimination in the feces ranged between 78 and 94% and in the urine between 8 and 21%. Difenoconazole did not accumulate to any appreciable extent since tissues contained less than 1.0% of the radioactivity after 7 days post dosing.

Difenoconazole undergoes successive oxidation and conjugation reactions. There is saturation of the metabolic pathway at high doses. The distribution, metabolism and excretion of difenoconazole are not sex dependent.

The overall quality of the toxicology database is good. Confidence in the hazard and dose response assessment is also good. There are no data toxicology data gaps.

Tables 1 and 2 summarize the toxicity studies and the categories of toxicity of this chemical.

Table 1 - Acute Toxicity of Difenoconazole Technical

Guideline No.	Study Type	MRID #s	Results	Toxicity Category
81-1	Acute Oral	42090006	LD ₅₀ ≈ 1453 mg/kg	III
81-2	Acute Dermal	42090007	LsD ₅₀ ≈ >2010 mg/kg	III
81-3	Acute Inhalation	42090008	LC ₅₀ ≈ >3300 mg/m ³ [4 hrs. Exposure]	IV
81-4	Primary Eye Irritation	42090009	mild eye irritation reversible in 7 days	III
81-5	Primary Skin Irritation	42090010	slight irritant	IV
81-6	Dermal Sensitization	42090011 42710004	negative	NA

Table 2 - Subchronic/Chronic/Mutagenicity /Metabolism/Toxicity of Difenoconazole

Study Type	MRID #	Results
21-day dermal toxicity-rabbit	42090013	NOAEL=10 mg/kg/day LOAEL=100 mg/kg/day
13 week feeding mouse	42090021	NOAEL=2 mg/kg/day LOAEL=30.8 mg/kg/day
13 week feeding rat	42090022	NOAEL=1 mg/kg/day LOAEL= 37.5 mg/kg/day
26 week oral feeding dogs	42090012	NOAEL=31.3 mg/kg/day LOAEL=96.6 mg/kg/day
carcinogenicity study mouse	42090015 42710006	NOAEL(systemic)=4.7 mg/kg/day LOAEL(systemic)= 46.3 mg/kg/day liver tumors in males/females
chronic toxicity/carcinogenicity in the rat	42090019 42090020	NOAEL=0.96 mg/kg/day LOAEL=24.12 mg/kg/day no evidence of carcinogenicity
chronic toxicity study dog	42090014 42710005	NOAEL=3.4 mg/kg/day LOAEL=16.4 mg/kg/day
developmental toxicity rat	42090016	maternal NOAEL=20 mg/kg/day LOAEL=100 mg/kg/day developmental NOAEL=100 mg/kg/day LOAEL=200 mg/kg/day
developmental toxicity rabbit	42090017	maternal NOAEL=25 mg/kg/day LOAEL=75 mg/kg/day developmental NOAEL=25 mg/kg/day LOAEL=75 mg/kg/day
reproductive toxicity	42090018	parent NOAEL=1.25 mg/kg/day LOAEL=12.5mg/kg/day offspg NOAEL=1.25 mg/kg/day LOAEL=12.5mg/kg/day
gene mutation-Salmonella	42090025	non-mutagenic +/- activation
gene mutation-E.coli	42710011	non-mutagenic +/- activation
micronucleus assay	42710012	non-mutagenic
DNA repair assay	42710012	non-mutagenic +/- activation
metabolism rat	42090028-31 42710013-14	Distribution, metabolism, excretion not sex dependent. 78-94% found in feces and 8-21% in urine. No accumulation. Negligible residues in tissues at 7 days. Peak absorption at 24- 48 hrs. Saturation of metabolic pathway at high doses.

3.2. FQPA Considerations

There are no exposure or toxicity data gaps in the consideration of the FQPA SF. The FQPA SFC met on October 19, 1998 to evaluate the hazard and exposure data for difenoconazole to ensure the protection of infants and children from exposure to this chemical. The FQPA SFC recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) should be reduced to a 1x factor. The FQPA SFC recommended that the 10x safety factor be removed since: 1) the toxicology database is complete; 2) there is no indication of increased susceptibility of rat or rabbit fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity data; 3) unrefined (Tier 1) dietary exposure estimates are protective since they will exaggerate dietary exposure estimates; 4) in the absence of complete environmental fate data for difenoconazole and to be protective to infants and children, worst-case fate parameters will be used in the EFED models for ground and surface source drinking water exposure assessments resulting in estimates that are upper-bound concentrations; and 5) there are currently no registered residential uses for difenoconazole and therefore, exposure to infants and children is not expected (Memo, B. Tarplee, 10/28/98). A copy of the FQPA SFC report is attached to this memorandum (Attachment 1).

3.3. Other FQPA Considerations

3.3.1. Cumulative Risk

EPA does not have, at this time, available data to determine whether difenoconazole has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that difenoconazole has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether difenoconazole share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for difenoconazole need to be modified or revoked.

3.3.2. Endocrine Disruption

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of difenoconazole and its end-use products for endocrine effects may be required.

3.4. Dose Response Assessment

On September 8, 1998, the HIARC evaluated the toxicology data base of difenoconazole, reconfirmed the RfD, addressed the potential enhanced sensitivity to infants and children as required by the FQPA of 1996, and selected the toxicological endpoints for acute and chronic dietary as well as occupational exposure risk assessments (there are no residential uses at this time for difenoconazole). A copy of the HIARC report is attached to this memorandum (Attachment 2). The FQPA SFC met on October 19, 1998 and addressed the potential enhanced sensitivity to infants and children as required by FQPA and recommended for reduction of the 10x FQPA SF to 1x.

An aRfD of 0.25 mg/kg was established for the subpopulation group, females 13+ years old only, based on a NOAEL of 25 mg/kg from a developmental toxicity study in the rabbit. Effects at the next higher dose level of 75 mg/kg (LOAEL) were based on post-implantation loss and resorptions per doe and a significant decrease in fetal body weight. These effects are presumed to occur after a single exposure *in utero* and therefore are considered to be appropriate for this risk assessment. **The aPAD and aRfD are equivalent (0.25 mg/kg) since the FQPA SFC reduced the 10x factor to 1x.** An acute dose and endpoint were not selected for the general population group (including infants and children) because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure [dose].

The cRfD of 0.01 mg/kg/day was determined on the basis of a two year chronic feeding oncogenicity study in the rat. The NOAEL of 0.96 mg/kg/day (equal to 1.0 mg/kg/day) was based on cumulative decreases in body weight gains at the LOAEL of 24.12 mg/kg/day (500 ppm). This cRfD was originally established at an RfD meeting in 1994 and was reconfirmed by the HIARC on September 8, 1998 (Memo, A. Kocialski and Jess Rowland 9/25/98). **The cPAD and the cRfD are equivalent (0.01 mg/kg/day) since the FQPA SFC reduced the 10x factor to 1x.**

A short-term dermal dose/endpoint was chosen from a developmental rabbit study. The HIARC selected an oral NOAEL of 25 mg/kg/day based on post-implantation loss, increased resorptions per dose, and decreased body weight seen at 75 mg/kg/day (LOAEL). An intermediate-term dermal endpoint was chosen from a two-generation reproduction rat study. The HIARC selected an oral NOAEL of 1.25 mg/kg/day based on decreased pup weight on day 21 at 12.5 mg/kg/day (LOAEL). A long-term dermal endpoint was not identified by HIARC because long-term dermal exposure is not expected based on a one time application as a seed treatment.

An inhalation dose/endpoint was not identified by HIARC because there is minimal concern for potential inhalation exposure/risk based on the low acute toxicity (Toxicity Category IV), application rate, application method, and number of applications [1x].

The CPRC met on May 18, 1994 to discuss and evaluate the weight of evidence on the carcinogenic potential of difenoconazole. The CPRC concluded that difenoconazole should be classified as a Group C - **possible human carcinogen** and recommended for the purpose of risk assessment, the margin-of-exposure (MOE) approach be used for the

quantification of human risk (Memo, Jess Rowland and Esther Rinde, 7/27/94).

The decision to classify difenoconazole as a Group C carcinogen was based on statistically significant increases in liver adenomas, carcinomas, and combined adenomas and carcinomas in both sexes of CD-1 mice, only at doses that were considered to be excessively high for carcinogenicity testing. The MOE approach was recommended because there was only very weak (limited) evidence of carcinogenic potential at dose levels not considered to be excessive, with significant changes observed only at excessive doses. In addition there was no evidence of genotoxicity. However, at this time, HED has not defined the level of concern for cancer risk using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the Q_1^* approach. The Q_1^* was determined to be 0.157 (mg/kg/day)⁻¹. This value incorporates the $\frac{3}{4}$ scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunsman, 12/8/98).

Table 3 presents the toxicological doses and endpoints.

Table 3 - Summary of Toxicological Doses and Endpoints of Difenoconazole

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary [females 13+ years old]	NOAEL= 25 UF = 100 FQPA SF = 1	post-implantation loss, increased resorptions per doe, decreased body weight	developmental rabbit
		aRfD = 0.25 mg/kg aPAD = 0.25 mg/kg	
Acute Dietary (General Population including infants and children)	None	An endpoint attributable to a single exposure (dose) for the general population was not available from the oral toxicity studies including the rat and rabbit developmental toxicity studies.	
Chronic (non-cancer) Dietary	NOAEL = 0.96 UF = 100 FQPA SF = 1	cumulative decreases in body weight gains	chronic/onco rat
		cRfD = 0.01 mg/kg/day cPAD = 0.01 mg/kg/day	
Chronic (cancer) Dietary	Group C (likely human carcinogen) $Q^* = 1.57 \times 10^{-1} \text{ (mg/kg/d)}^{-1}$		mouse oncogenicity study
Short-Term ^a (Dermal)	oral NOAEL = 25	post-implantation loss, increased resorptions per doe, decreased body weight	developmental rabbit
Intermediate-Term ^a (Dermal)	oral NOAEL=1.25	based on decreased pup weight on day 21	2-generation reproduction rat
Long-Term (Dermal) ^a Non Cancer	None	Long-term dermal exposure is not expected based on a one time application as a seed treatment. This risk assessment is not required.	

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Long-Term Oral and Dermal ^a (Cancer)	$Q_1^* = 0.157$	Difenoconazole is classified as a Group C, possible human carcinogen with the recommendation of a non-linear (MOE) approach for human risk characterization using the NOAEL of 4.7 mg/kg/d from mouse oncogenicity study. (CPRC Document, 7/27/94). However, at this time, the Agency has not defined the level of concern for cancer risk using the MOE approach. Therefore, a quantitative risk analysis was conducted utilizing the Q_1^* approach. The Q_1^* was determined to be 1.57×10^{-1} (mg/kg/day) ⁻¹ . This value incorporates the 3/4 scaling factor and is based on the male mouse liver adenomas and/or carcinomas combined (Memo, Lori Brunsman, 12/8/98).	
Inhalation (Any time period)	None	Based on the low acute toxicity [Toxicity Category IV], the application rate, the application method, and the number of applications [1x] there is minimal concern for potential inhalation exposure/risk. This risk assessment is not required for the non-cancer endpoint.	

^a A dermal absorption factor of 75% should be used for route-to-route extrapolation.

4.0 EXPOSURE ASSESSMENT

4.1. Summary of Proposed Uses

Helix™ is a ready to use liquid formulation and is intended as a seed treatment. An EPA approved coloring agent, [REDACTED], has been added to the formulation. No additional coloration, dyes, binders, or water are needed. Helix™ is a multi-active ingredient formulation. Besides difenoconazole, it is comprised of thiamethoxam (insecticide), (R)-[(2,6-dimethylphenyl)-methoxyacetylaminol]-propionic acid methyl ester (fungicide), and fludioxonil (fungicide). Fludioxonil (40 § CFR 180.516) and (R)-[(2,6-dimethylphenyl)-methoxyacetylaminol]-propionic acid methyl ester (40 CFR § 180.408, used in place of metalaxyl (Memo, D223261, L. Kutney, 4/24/96)) are registered for use on canola. The thiamethoxam use in/on canola will be addressed in a separate document.

Treated seeds shall be labeled as such. Helix™ is not to be used on agricultural establishments in hopper boxes, planter boxes, slurry boxes, or other seed treatment applications at or immediately before planting.

Helix™ is applied using standard slurry seed treatment equipments. The maximum application rate is 23 fl. oz./100 lbs. of seed or 0.025 lbs. ai/100 lbs. of seed.

Inert ingredient information may be entitled to confidential treatment

4.2. Dietary Exposure

4.2.1. Food Exposure

The following information is from reviewed data (Memo, S. Chun, D252644, 10/5/99) unless otherwise cited.

4.2.1.a. Nature of the Residue

Plants: The nature of the residue in plants is understood. Plant metabolism studies were conducted on wheat, tomatoes, grapes, potatoes, and canola and found to be acceptable (Memos, G. Kramer, D203644, 6/16/94; R. Lascola, D172067, 10/26/92; G. Kramer, D216521, 2/23/96; S. Chun, D252644, 10/5/99). The canola metabolism study was performed using a foliar application of difenoconazole on canola. The proposed use is a seed treatment. The results in these studies are consistent with foliar metabolism studies submitted and reviewed for wheat, tomatoes, and potatoes. The metabolic pathway in canola appears to proceed by hydrolysis of the ketal to the ketone followed by reduction of the ketone to the alkanol (CGA 205375). CGA 205375 can be conjugated with sugars or the bridge linking the phenyl and triazole moieties is cleaved forming free triazole (CGA 7019). CGA 7019 can be conjugated with serine to yield CGA 131013, which can be oxidatively deaminated to the lactic acid analogue and eventually degraded to CGA 142856. There was no evidence for a minor metabolic pathway via hydroxylation of the phenyl ring moiety.

Metabolism studies for a wheat seed treatment have been submitted and reviewed (Memo, D1948412, G. Kramer, 3/28/94). The seed treatment metabolism studies had similar results to the foliar studies. Therefore, HED will translate the foliar canola studies to seed treatment and consider the nature of the residue in canola understood.

Animals: The nature of the residue in animals was considered understood for the purposes of petition 2F4107 **only** (Memo, G. Kramer, D203644, 6/16/94). It was concluded that for any future petition in which there is a greater potential for transfer of residues to meat and milk, additional animal metabolism studies would be required. Since the proposed use on canola is a seed treatment and canola is not a major feed item, there is no greater potential for transfer of residues to meat and milk. Therefore, additional animal metabolism studies will not be required for this action and the nature of the residue in animals will be considered understood for this action.

The HED Metabolism Assessment Review Committee (MARC) met on July 14, 1994 to discuss the toxicological significance of potential metabolites. It was decided that none of the difenoconazole metabolites warrant inclusion in the tolerance regulation, separate regulation, inclusion in the dietary risk assessment, additional metabolism studies, or additional toxicological studies. The triazole metabolites have previously been determined not to be of toxicological concern in conjunction with tebuconazole. This conclusion can be expanded to include triazole propanoic acid (Alberto Protzel, Personal Communication 1/17/95) (Memo, Kramer,

D210080, 1/18/95). CGA-205375 was determined not to be of concern due to the low potential for residues associated with seed treatment (Memo, G. Kramer, 7/22/94). However, if in the future the petitioner wishes to propose tolerances for difenoconazole resulting from foliar uses which result in higher residue levels, the MARC will reconsider whether CGA-205375 needs to be included in the difenoconazole tolerance expression. If CGA-205375 is included in the tolerance expression, then new analytical enforcement methodology and a second lab validation will be required. If quantifiable levels of residues are found in animal feed items, then animal feeding studies will be required (Memo, G. Kramer, 7/22/94).

4.2.1.b. Residue Analytical Methods

Plants: The petitioner has submitted a copy of Method AG-676. Method 676 is similar to the enforcement method for wheat, Method 575; therefore, an Independent Laboratory Validation (ILV) was not required. Acceptable recoveries were obtained for all matrices. Samples are homogenized and centrifuged with an ACN/hexane mixture. The resulting solution is decanted and extracted with ACN/hexane (1:1). The hexane layers are combined and back extracted with ACN. The ACN fractions are combined and brought up to volume. A 40 mL aliquot is taken and evaporated to 0.5 mL. An ACN/water mixture is added and the resulting mixture eluted by SPE. The final eluate in methanol is reduced to 2.5 mL and brought to volume (5 mL) with water. The sample is analyzed by GC/MSD. The reported limit of quantitation (LOQ) is 0.01 ppm.

A Petition Method Validation (PMV) on canola seed has been requested (Memo, D258772, S. Chun, 9/3/99). **The PMV has not been completed. HED concludes that Method 676 is adequate for data gathering purposes. A final conclusion on the adequacy of Method 676 for enforcement of the proposed tolerances will be withheld pending submission a satisfactory method validation by the Analytical Chemistry Laboratory (ACL).**

Animals: The petitioner proposed Method AG-544A, "Difenoconazole (CGA-169374) Analytical Method for the Determination of CGA-169374 Residues in Dairy and Poultry Tissue, Eggs and Milk by Gas Chromatography," as the analytical enforcement method. The sample is extracted by homogenization for 1 minutes with 95:5 acetonitrile:concentrated ammonium hydroxide. After filtration, the extract is diluted with water and saturated NaCl and partitioned with hexane. The hexane fraction is partitioned with acetonitrile and the acetonitrile fraction is cleaned-up on a silica gel SepPak. The final extract is analyzed by packed column GC using alkali flame ionization detection (Memo, G. Kramer, D194842, 3/30/94). The reported LOQ for livestock tissue is 0.05 ppm; the reported LOQ for milk is 0.01 ppm.

HED concluded that Method AG-544A is adequate for enforcement purposes. An ILV of the method was submitted and a satisfactory PMV by ACL was completed (Memo, G. Kramer, D205118, 7/20/94). The method was forwarded to the Food and Drug Administration (FDA) to be included in the Pesticide Analytical Manual II (PAMII).

4.2.1.c. Multi-Residue Method

The results of Multiresidue testing of difenoconazole and its metabolites, CGA-189138, CGA-205374, and CGA-205375, (MRID# 420900-54) have been forwarded to FDA (Memo, R. Lascola, 5/21/92). The study is entitled "Multiresidue Method Testing of CGA-169374 and Metabolites in Crops and Animal Tissues", CIBA-GEIGY Project No. ABR-89048, by R. K. Williams, CIBA-GEIGY Corporation, Greensboro, NC; 7/20/92; MRID# 420900-54. Compounds investigated included CGA-169374, CGA-205374, CGA-205375, and CGA-189138. The petitioner concluded that Protocols C, D, and E did not yield sufficient recoveries or responses to be useful for the detection of these chemicals. Protocol A (N-methyl carbamates) does not apply to these chemicals. Protocol B (acids and phenols) only applies to CGA-189138, however recovery of that compound was not tested (Memo, R. Lascola, D172067, 10/22/92).

4.2.1.d. Storage Stability

Storage stability data were submitted and found to be acceptable. These data indicate that residues of difenoconazole are stable in frozen canola seed for periods up to 331 days (~11 months).

4.2.1.e. Crop Field Trials

A total of 6 field trials were submitted and reviewed. The residue levels of difenoconazole in canola seed were all less than the limit of quantitation (LOQ) of 0.01 ppm. The submitted data indicate that residues of difenoconazole will not exceed the proposed tolerance level of 0.1 ppm for canola. However, the appropriate tolerance level for "canola, seed" is 0.01 ppm. **A revised Section F should be submitted.**

4.2.1.f. Processed Food/Feed

No processing study is required for this petition. The maximum theoretical concentration factor for canola to canola oil is 3x (Guidelines 860.1520, Table 3). Difenoconazole was applied to canola at an exaggerated rate of 3.6x (0.09 lb a.i./100 lbs seed) as a seed treatment in 2 locations. Residue levels for each location were below the limit of quantitation (LOQ) of 0.01 ppm.

4.2.1.g. Meat, Milk, Poultry, Eggs

The petitioner had requested (in support of wheat use, PP#2F4107) a waiver for animal feeding studies based on the low potential for residues in feed items and the exaggerated rates used in the animal feeding studies. Based on a diet comprised of 100% wheat raw agricultural commodities (RACs) and residues at the level of the proposed tolerances, the maximum dietary burden for dairy cattle is estimated to be 0.30 ppm. Two metabolism studies were performed on ruminants (lactating goats) in a 10-day study with a dose rate of 4.17 ppm (14x the 0.30 ppm estimated dietary

burden) and a 3-day study with a dose rate of 100 ppm (333x the 0.30 ppm estimated dietary burden). The total radioactive residue (TRR) in the goat tissues was used to estimate the expected residues in a feeding study with a dose rate of 0.30 ppm. The maximum residue observed was in liver, estimated to be at a level of 0.02 ppm from both metabolism studies. This value is 2.5x below the LOQ of the proposed analytical enforcement method (0.05 ppm). The estimated residue in milk would be 0.5 ppb, 200x below the method LOQ of 0.1 ppm. HED accepted the petitioner's proposal to allow the animal metabolism studies to also serve as feeding studies. Feeding studies in cattle and poultry, as appropriate, will be needed for any future tolerance request which could result in higher residues of concern in meat, milk, poultry, and eggs (Memo, G. Kramer, D194842, 3/30/94).

The proposed use in/on canola in this action does not appear to result in higher residues of concern in meat, milk, poultry, and eggs. The proposed use pattern (seed treatment) and low animal dietary feed consumption (canola meal only commodity consumed, 15% of diet) support the assumption of no increase in residues. Therefore, animal feeding studies are not required for this action with the same caveat that if, in the future, uses are proposed resulting in higher residues in animal commodities, feeding studies will be required.

4.2.1.h. Anticipated Residues

Anticipated residues (ARs) were calculated from field trial data (Memo, S. Chun, D253277, 3/11/99). An AR of 0.005 ppm ($\frac{1}{2}$ LOQ) will be used for canola oil based on field trial data. Table 4 presents the ARs to be used in the chronic (non-cancer and cancer) dietary analyses only.

Table 4 - Summary of Difenconazole Anticipated Residues for Dietary Risk Assessment

Commodity	Anticipated Residue Levels to Use in Chronic (non-cancer, and cancer) DEEM™ Analyses (ppm)
Bananas	0.01
Plantains	0.01
Canola	0.005
Wheat grain	0.005
Sweet Corn	0.005
Meat*	0.000014
Meat by-products (except kidney)*	0.00044
Kidney*	0.00012
Fat*	0.000041
Milk	0.000013
Poultry meat	0.000006
Poultry meat by-products (except kidney)	0.000023
Poultry kidney	0.000034
Poultry fat	0.0000030
Eggs	0.000019

Table 4 - Summary of Difenoconazole Anticipated Residues for Dietary Risk Assessment

Commodity	Anticipated Residue Levels to Use in Chronic (non-cancer, and cancer) DEEM™ Analyses (ppm)
Egg whites	0.0000043
Egg yolk	0.000046

*These ARs should be used for meat, fat and meat by-products of cattle, horses, goats, hogs, and sheep in the DEEM run.

To provide for the re-evaluation of the ARs, the Agency will require under Section 408(b)(2)(E) that additional residue data be submitted within five years.

4.2.1.i. Confined Accumulation in Rotational Crops

The nature of the residue is understood. The data indicate that the phenyl/triazole bridge of difenoconazole is cleaved in the soil and that triazole-specific metabolites are preferentially taken up by the rotational crops. The maximum TRR observed with phenyl-labeled difenoconazole was 0.009 ppm (wheat stalks) and with triazole-labeled difenoconazole 0.314 ppm in wheat grain (Memo, G. Kramer, D210080, 1/18/95). The registrant has submitted the results of two confined rotational studies using phenyl-labeled difenoconazole. In the RACs of all rotational crops planted 30-33 days after application of difenoconazole, the TRR was <0.01 ppm. These results support the proposed 30-day plantback restrictions for all rotational crops (Memo, G. Kramer, D217119, 9/13/95).

A 30-day plantback restriction for all crops is appropriate. The label proposes a 30-day plantback for certain crops and a 120-day plantback interval for all others. This restriction is based on data submitted for the other active ingredients and represents the most restrictive plantback interval.

4.2.1.j. Codex Harmonization

There is neither a Codex proposal, nor Canadian or Mexican maximum residue limits (MRLs) for residues of difenoconazole in canola. Therefore, a compatibility issue is not relevant to the proposed tolerance. A copy of the International Residue Limit Sheet (IRLS) is attached to this memorandum (Attachment 4).

4.2.2. Dietary Exposure Estimate

A dietary exposure analysis using the Dietary Exposure Evaluation Model (DEEM™) was completed (Memo, S. Chun, D258775, 10/12/99) for acute and chronic (non-cancer and cancer) dietary exposure. The DEEM™ analyses evaluated the individual food consumption as reported by respondents in the USDA 1989-92 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical from each commodity. The complete analyses are attached (Attachment 3).

Acute Dietary

For the acute dietary analysis, an aPAD of 0.25 mg/kg (incorporating 10x for interspecies extrapolation, 10x for intraspecies variability, and 1x FQPA SF) was used for the population subgroup, females 13-50 years old only. The acute dietary analysis for difenoconazole is a conservative estimate of dietary exposure (Tier 1 assessment) with the use of tolerance level residues and 100%CT. Table 5 summarizes the acute dietary exposure.

Table 5 - Acute Dietary Exposure Results

Subgroups ¹	aPAD (mg/kg)	95 th Percentile		99 th Percentile		99.9 th Percentile	
		Exposure (mg/kg)	% aPAD	Exposure (mg/kg)	% aPAD	Exposure (mg/kg)	% aPAD
Females (13+ years old/pregnant/nn)	0.25	0.000852	< 1	0.001093	< 1	0.001265	< 1
Females (13+ years old/nursing)	0.25	0.000889	< 1	0.001086	< 1	0.001115	< 1
Females (13-29 years old/np/nn)	0.25	0.000750	< 1	0.001008	< 1	0.001570	< 1
Females (20+ years old/np/nn)	0.25	0.000668	< 1	0.000987	< 1	0.001359	< 1
Females (13-50 years old)	0.25	0.000701	< 1	0.001008	< 1	0.001436	< 1

¹ nn= not nursing; np = not pregnant

The percent aPADs found in this analysis were below HED's level of concern at the 95th percentile for all females 13-50 years old subgroups with all exposures <1% aPAD. HED's level of concern is for exposures >100 % aPAD. The results of this analysis indicate that the estimated acute dietary exposure associated with the existing and new use (canola) of difenoconazole is below HED's level of concern.

Chronic (Non-Cancer and Cancer) Dietary

For the chronic dietary analysis, a cPAD of 0.01 mg/kg/day (incorporating 10x for interspecies extrapolation, 10x for intraspecies variability, and 1x FQPA Safety Factor) was used. The chronic (non-cancer and cancer) dietary analyses for difenoconazole are somewhat refined estimates (Tier 3 assessment) with the use of ARs for all commodities and %CT information. Table 6 summarizes the chronic (non-cancer) dietary exposure.

Table 6 - Chronic (non-cancer) Dietary Exposure Results

Subgroups ^{1,2}	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.000005	< 1
All infants (<1 year old)	0.000016	< 1
Nursing infants (< 1 year old)	0.000007	< 1
Non-nursing infants (< 1 year old)	0.000019	< 1
Children (1-6 years old)	0.000011	< 1
Children (7-12 years old)	0.000005	< 1
Females (13-19 years old/np/nn)	0.000003	< 1
Females (20+ years old/np/nn)	0.000004	< 1
Females (13-50 years old)	0.000004	< 1
Females (13+years old/preg/nn)	0.000004	< 1
Females (13+years old/nursing)	0.000006	< 1
Non-Hispanic whites	0.000006	< 1
Non-Hispanic/Non-white/Non-black	0.000006	< 1

¹ Population subgroups shown include the U.S. general population, all infants and children subgroups, all females 13-50 subgroups, and any other population subgroup whose exposure exceeds that of the U.S. general population.

² np= not pregnant; nn = not nursing

The %cPADs were below HED's level of concern for the U.S. population and all subgroups with all exposures <1% cPAD. HED's level of concern is for exposure >100 % cPAD. The results of this analysis indicates that the estimated chronic dietary exposure associated with the existing and new use (canola) of difenoconazole is below HED's level of concern.

Chronic (Cancer) Dietary Risk:

A Q_1^* of $0.157 \text{ (mg/kg/day)}^{-1}$ was calculated. HED generally considers 1×10^{-6} as negligible risk (i.e, less than 1 in 1 million) for cancer. The results of this analysis indicate that the cancer dietary risk of 8.6×10^{-7} associated with the proposed use of difenoconazole is below the Agency's level of concern. Table 7 summarizes the chronic (cancer) dietary exposure.

Table 7- Chronic (non-cancer) Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	Lifetime Cancer Risk ¹
U.S. Population	0.000005	8.6×10^{-7}

$$\begin{aligned}
 \text{Lifetime Risk} &= 70\text{-year Lifetime Exposure (mg/kg/day)} \times Q_1^* \\
 &= (0.000033 \text{ mg/kg/day}) \times (1.6 \times 10^{-2} \text{ (mg/kg/day)}^{-1})
 \end{aligned}$$

4.2.3 Water

HED and EFED do not have monitoring data available to perform a quantitative drinking water risk assessment for difenoconazole at this time. EFED provided ground and surface water exposure estimates for difenoconazole (parent compound only) to be used qualitatively.

Since GENEEC and SCI-GROW are not designed to estimate runoff or leaching for seed treatment pesticides, there are uncertainties in the predictive potential of the Tier 1 modeling. Additional uncertainties are associated with the use of unreviewed “screened” environmental fate data. It was necessary to use screened environmental fate data in the assessment because there was insufficient time to conduct a formal data review before the Registration Division (RD) due date. The noted uncertainties in the water assessment, however, are not expected to substantially decrease the conservativeness of the Tier 1 modeling results (Memo, J. Hetrick, 2/9/99). This Tier 1 modeling was done in support of a previous petition for wheat (PP# 2F4107). Because wheat is seeded in fields at a higher rate than canola, the wheat Tier 1 water modeling will be used in support of this petition, as its scenario provides a more conservative estimate.

Other uncertainties in the model assessments are associated with the application rate of difenoconazole. The maximum seeding rate for wheat (120 lbs wheat seed/A) was used to calculate the maximum difenoconazole application rate. EFED notes that the planting rates for wheat can range from 60 to 120 lbs seed/A (Memo, J. Hetrick, 2/9/99). Canola seed is planted at rates of 5-10 lbs seed/A.

4.2.3.a. Input Assumptions and Parameters

The application rate of difenoconazole is based on a wheat seed treatment rate of 0.025 lbs a.i./100 lbs (EPA Reg. No. 100-778) and of maximum seeding rate 120 lbs seed/A. Therefore, the maximum difenoconazole application rate is 0.03 lbs ai/A. Based on a preliminary screen of the environmental fate data, difenoconazole is expected to be relatively immobile and persistent in terrestrial environments. The adsorption coefficient for difenoconazole is 12.76 mL/g ($K_{oc}=3866$) in an agricultural sand, 62.97 mL/g ($K_{oc}=3470$) in sandy loam soil, 54.84 mL/g ($K_{oc}=7734$) in silt loam soil, and 47.18 mL/g ($K_{oc}=7,734$) in a silty clay loam soil. The aerobic soil metabolism half-life for difenoconazole ranged from 175 to 1600 days. Difenoconazole had a first-order photo degradation half-life of 5.68 days in water (Memo, J. Hetrick, 2/9/99).

Surface Water

GENEEC is a single event model (one runoff event), but can account for spray drift from multiple applications. GENEEC is hardwired to represent a 10 ha field immediately adjacent to a 1 ha pond, 2 m deep with no outlet. The pond receives a spray drift event from each application plus one runoff event, which moves a maximum of 10% of the applied pesticide into the pond. This runoff can be reduced by degradative processes in the field and by the effects of binding to soil in the field. In the GENEEC model, spray drift is equal to 1% of the applied for ground spray

application and 5% for aerial application.

GENEEC does have certain limitations and is not an ideal tool for use in drinking water risk assessments. Surface-water-source drinking water tends to come from bodies of water that are substantially larger than a 1 hectare pond. Furthermore, GENECC assumes that essentially the whole basin receives an application of the chemical. In virtually all cases, basins large enough to support a drinking water facility will contain a substantial fraction of area which does not receive the chemical. Furthermore, the persistence of the chemical near the drinking water facility is usually overestimated because there is always at least some flow in a river or turn over in a reservoir or lake.

Although GENECC does have these limitations, it can be used in screening calculations and does provide an upper bound on the concentration of pesticide that can be found in drinking water. If a risk assessment based on GENECC does not exceed the level of concern, then the actual risk is not likely to be exceeded. However, since GENECC can substantially overestimate true drinking water concentrations, it will be necessary to refine the GENECC estimate when the level of concern is exceeded. In those situations where the level of concern is exceeded and the GENECC value is a substantial part of the total exposure, EFED can use a variety of methods to refine the exposure estimates.

Ground Water

SCI-GROW (Screening Concentration In Ground Water) is an empirical screening model based on actual ground water monitoring data collected from small-scale prospective ground water monitoring studies for the registration of a number of pesticides that serve as benchmarks for the model. The current version of SCI-GROW provides realistic estimates of pesticide concentrations in shallow, highly vulnerable ground water (i.e., sites with sandy soils and depth to ground water of 10 to 20 feet). There may be exceptional circumstances under which concentrations of a pesticide may exceed the SCI-GROW estimates; however, such exceptions should be rare since the SCI-GROW model is based exclusively on ground water concentrations resulting from studies conducted at sites (shallow ground water and coarse soils) and under conditions (high irrigation) most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW are based on the largest 90-day average concentration recorded during the sampling period. Because of the conservative nature of the monitoring data on which the model is based, SCI-GROW provides an upper bound estimate of pesticide residues in water. Because of the belief that pesticide concentrations in ground water do not fluctuate widely, SCI-GROW provides one concentration estimate to be used as a maximum and an average pesticide concentration value in ground water.

4.2.3.b. Surface Water Estimates

Surface water estimates were made using the GENEEC model and available fate data for difenoconazole. EFED calculated the following Tier 1 Estimated Environmental Concentrations (EECs) for difenoconazole in surface water:

Acute or peak EECs: 0.125 ppb
Chronic (56-day) EECs: 0.048 ppb

Note: According to OPP drinking water guidance (HED SOP 99.5), the 56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment would be 0.016 ppb.

4.2.3.b. Ground Water Estimates

Using the SCI-GROW model to estimate concentrations in ground water for the parent, the following EEC was calculated:

Ground water: 0.00084 ppb

This concentration can be considered as both the acute and chronic value.

4.2.3.c. Drinking Water Level of Comparisons

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

HED's default body weights are: males - 70kg, females - 60kg, and children - 10 kg. HED's default consumptions are: males - 2 L, females - 2 L and children - 1 L.

$$DWLOC (\mu g/L) = \frac{\text{water exposure (mg/kg/day)} \times (\text{body weight})}{\text{consumption (L)} \times 10^{-3} \text{ mg}/\mu g}$$

Acute

HED has calculated DWLOCs for acute exposure to difenoconazole in surface and ground water for females, 13-50 years old. To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEM™ analysis) was subtracted from the aPAD to obtain the acceptable acute exposure to difenoconazole in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures. Table 8 summarizes the acute DWLOCs.

Table 8 - Acute DWLOCs

Subgroups¹	DWLOC (ppb)
Females (13+ years old/pregnant/nn)	7470
Females (13+years old/nursing)	7470
Females (13-29 years old/np/nn)	7480
Females (20+ years old/np/nn)	7480
Females (13-50 years old)	7480

nn= not nursing; np = not pregnant

Chronic (non-cancer)

HED has calculated DWLOCs for chronic (non-cancer) exposure to difenoconazole in surface and ground water. To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from the DEEM™ analysis) was subtracted from the cPAD to obtain the acceptable chronic exposure to difenoconazole. DWLOCs were then calculated using default body weights and drinking water consumption figures. Table 9 summarizes the chronic (non-cancer) DWLOCs.

Table 9 - Chronic (non-cancer) DWLOCs

Subgroups^{1,2}	DWLOC (ppb)
U.S. Population (48 states)	350
All infants (<1 year old)	100
Nursing infants (< 1 year old)	100
Non-nursing infants (< 1 year old)	100
Children (1-6 years old)	100
Children (7-12 years old)	100
Females (13-19 years old/np/nn)	300
Females (20+ years old/np/nn)	300
Females (13-50 years old)	300
Females (13+ years old/preg/nn)	300
Females (13+ years old/nursing)	300
Non-Hispanic whites	350
Non-Hispanic/Non-white/Non-black	350

- ¹ Population subgroups shown include the U.S. general population, all infants and children subgroups, all females 13-50 years old subgroups, and any other population subgroup whose exposure exceeds that of the U.S. general population.
- ² np= not pregnant; nn = not nursing

Chronic (cancer)

HED has calculated DWLOCs for chronic (cancer) exposure to difenoconazole in surface and ground water for the U.S. Population. To calculate the DWLOC for chronic (cancer) exposure relative to a carcinogenic toxicity endpoint (Q_1^*), the chronic (cancer) dietary food exposure (from the DEEM™ analysis) was subtracted from the ratio of the negligible cancer risk (1×10^{-6}) to the Q_1^* to obtain the acceptable chronic (cancer) exposure to difenoconazole in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures. The DWLOC_{cancer} for U.S. population is **0.048 ppb**.

4.3 Occupational Exposure

The current occupational exposure assessment is based on data and assumptions used for a previous assessment for difenoconazole on wheat seed (Memo, Difenoconazole (**Dividend**®) in/on wheat and animal RACs, D.Vogel, 3/22/99). Potential exposures and risks from the use of difenoconazole on canola seeds are not expected to be higher than those for wheat seed.

4.3.1. Summary of Use Patterns and Formulations

This occupational exposure assessment addresses the use of difenoconazole in Helix™ (EPA reg. # 100-0GL), insecticide/fungicide combination product, which contains 1.25% of difenoconazole. Difenoconazole is a fungicide used as a systemic seed dressing to control certain seed-borne and soil-borne diseases. The product label specifies a maximum application rate of 0.025 pounds of difenoconazole per 100 pounds of seed.

4.3.2. Commercial Seed Treatment Exposures and Assumptions

In a typical seed treatment facility (Mr. Brad Russell of the Novartis Seed Treatment Facility, personal communication with Olga Odiott, 10/98), treatment is usually done using automatic and computerized equipment. In the case of difenoconazole, due to the small amount used, the fungicide is added manually (via graduated cylinder) to the treatment tank. In addition, seed treater, baggers and sewers are also part of the operation. The work area is supplied with aspirators to minimize any potential inhalation exposure. For difenoconazole, this activity is usually performed 5 days a week for 2 to 3 weeks, 3 times per year. HED's exposure assessment is based on the assumptions in Table 10.

Table 10 - Assumptions for Commercial Handler (i.e., Mixer/Operator, Bagger, Bag Sewer) Exposure Assessments

Factors	Quantities/Units		Source
Bag size	50 lbs.		Study: Worker Exposure to Apron Flowable While Treating Seed Commercially
Bags produced per hour	250		
Hours worked per day	8		
Personal Protective Equipment worn by Mixer, Bagger and Bag Sewer	Chemical apron, goggles, gloves for mixer only and long-sleeved-shirt and pants for bagger and sewer.		Study: Worker Exposure to Apron Flowable While Treating Seed Commercially
Mixer unit exposures (mg/kg ai handled)	Dermal: 0.0610	Inhalation: 0.000775	PHED version 1.1
Bag sewer unit exposures (mg/kg ai handled)	Dermal: 0.0346	Inhalation: 0.0056	
Bagger unit exposures (mg/kg ai handled)	Dermal: 0.0182	Inhalation: 0.000518	
Application rate	0.025 lb ai/100 lbs seed		label
Application Type	commercial mist-type seed treatment equipment		
Days worked per week	5		Mr. Brad Russell, Novartis Seed Treatment Facility
Days worked per year	45		

HED has very limited data for seed treatment scenarios. These exposure estimates for commercial seed treaters are based on data from a study entitled **Worker exposure to Apron Flowable while treating seed commercially** (Ciba-Geigy, 1993) submitted in support of MAXIM 4FS. This study was reviewed by HED in August of 1994 (Memo, B. Kitchens, 9/23/94).

This study determined the amount of active ingredient that mixer/operators, baggers and bag sewers were exposed to during the commercial treatment of seed. The study was considered supplemental but upgradable by HED, pending the registrant's response to questions concerning field recoveries and ambient conditions. However, the study is the best body of data available for commercial seed treatment operations. HED notes that although limited, data from the open literature suggests that overall, pesticide application of seed treatment in commercial environments is a relatively safe operation, with low expected exposures (Bulletin of Environ. Contam. Toxicol. 31, 244-250, Grey, Marthre and Rogers, 1983).

4.3.3. Commercial Seed Treater Exposure Assessment

Lifetime Average Daily Dose (LADD) calculations for commercial seed treaters were done assuming 5 days worked per week for 3 weeks, 3 times each year. The LADD calculation assumes that the individual would work 35 out of 70 years.

Based on use patterns, only short- and intermediate-term dermal exposures are expected. Both the short- and intermediate-term MOEs were greater than 100 and therefore, below HED's level of concern. Although an inhalation endpoint (any time-period) was not selected for difenoconazole, for purposes of the cancer risk calculations, inhalation exposures were estimated and added to the dermal exposures. The CPRC committee determined that an MOE approach was appropriate to determine cancer risk. However, at this time, the Agency has not defined the level of concern for cancer using the MOE approach. Therefore, the Q_1^* approach was used for calculating cancer risk. A Q_1^* of 0.157 was determined, based on the male mouse liver adenoma and/or carcinoma combined tumor rates (memo, Lori Brunsman, 12/8/98). Table 11 summarizes the HED/RAB1 estimates for exposure for commercial seed treaters including mixer/loaders, baggers and bag sewers.

Table 11 - Seed Treatment Exposure to Difenoconazole fungicide

Job Function	Dermal Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Inhalation Average Daily Dose (ADD) for Dividend™ mg ai/kg bw/day	Short-Term Dermal MOE	Intermediate-Term Dermal MOE	Lifetime Average Daily Dose (LADD) mg ai/kg bw/day	Cancer MOE	Cancer Risk (Q*)
Mixer/Operator	0.0087	0.00015	2.9×10^3	1.4×10^2	0.00054	8.7×10^3	8.5×10^{-5}
Bag Sewers	0.0049	0.0011	5.1×10^3	2.5×10^2	0.00037	1.3×10^4	5.8×10^{-5}
Bagger	0.0026	0.000098	9.7×10^3	4.8×10^2	0.00017	2.8×10^4	2.6×10^{-5}

The following equations were used to determine the expected worker exposures resulting from the commercial seed treatment applications of difenoconazole on canola.

$$\begin{aligned}
 \text{MOE short-term dermal} &= \frac{\text{NOAEL}(25 \text{ MG / KG / DAY})}{\text{ADD}} & \text{MOE intermediate-term dermal} &= \frac{\text{NOAEL}(1.25 \text{ MG / KG / DAY})}{\text{ADD}} \\
 \text{ADD} &= \left(\left(\text{UNIT EXPOSURE} \left(\frac{\text{MG}}{\text{KG AI}} \right) \right) \times \left(\frac{1 \text{ KG}}{2.2 \text{ LBS}} \right) \times \left(\text{APPLICATION RATE} \left(\frac{\text{LBS AI}}{100 \text{ LBS SEED}} \right) \right) \right) \\
 &\quad \times \left(\frac{\text{SEED}}{\text{BAG}} \right) \times \left(\frac{\text{BAGS}}{\text{HOUR}} \right) \times \left(\frac{\text{HOURS}}{\text{DAY}} \right) \times \left(\frac{1}{\text{BODY WEIGHT}(60 \text{ KG})} \right) \times 0.75(\text{dermal absorption}) \\
 \text{LADD} &= \text{ADD inhalation \& dermal} \times \left(\frac{\text{Days Worked per Year}}{\text{Total Days per Years}} \right) \times \left(\frac{35 \text{ Years Worked}}{70 \text{ Year Lifetime}} \right) \\
 \text{CANCER RISK} &= Q^* (0.157 \text{ mg / kg / day}) \times \text{LADD}
 \end{aligned}$$

Although there are uncertainties about the quality of the data, HED concludes that the potential risk

will not exceed the levels of concern. HED's level of concern for short and intermediate exposure to difenoconazole are for MOEs below 100. Estimated short- and intermediate-term dermal MOEs are well above 100. The exposure assessment is based on the best body of data that is available to HED at this time. HED notes that although limited, data from the open literature suggests that overall, pesticide application of seed treatment in commercial environments is a relatively safe operation, with low expected exposures (Bulletin of Environ. Contam. Toxicol. 31, 244-250, Grey, Marthre and Rogers, 1983).

The cancer risk for commercial seed treaters was determined to be 8.5×10^{-5} for the worst-case scenario. Generally, HED's level of concern for occupational exposure is for cancer risk greater than 1×10^{-4} . Therefore, the cancer risk for commercial seed treatment does not exceed HED's level of concern.

4.3.4. Farm Worker Exposures and Assumptions

Since canola is planted mechanically, the potential agricultural worker exposures to difenoconazole are expected to be minimal. Canola planting usually consists of two functions; mixer/loader and driver/planter. The highest exposure is expected for the mixer/loader scenario, which involves opening the treated seed bags and emptying the contents into the application equipment. The driver/planter is not expected to receive significant exposure.

PHED data was used to estimate exposure to workers. Currently, PHED does not contain data on this specific scenario. Therefore, the closest possible match is GRANULAR OPEN MIXING. The 'no gloves' unit exposure was used as a conservative assumption. The quality of the dermal data is considered '**low confidence**' (ABC grade, low replicates, and poor grade quality of hand replicates). The quality of the inhalation data is considered '**high confidence**' (AB grade, high replicates) (PHED v 1.1 Surrogate Table).

Typical canola planting-practice information, such as the number of acres that are planted per day and the pounds of seed planted per acre were obtained from the 1997 Agricultural Census and the USDA Crop Profiles website, respectively. The information considered in calculating exposure estimates is listed in Table 12.

Table 12 - Mixer/Loader Exposure Assumptions

Scenario	Exposure	Unit Exposure (mg/lb ai)	Application Rate	Pounds seed /Acre	Average farm size ¹	Body Weight (kg)
Mixer/Loader	Dermal	0.0084	0.025 lbs ai/100 lbs seed	10	200	60
Mixer/Loader	Inhalation	0.0017	0.025 lbs ai/100 lbs seed	10	200	60
Source	- -	PHED 1.1 Surrogate Table. Granular open pour, no gloves	Label	USDA Crop Profiles website	1997 Census of Agriculture	Default value

¹ This information was based on the average number of acres planted with canola divided by the number of farms growing canola in the United States. The relevant data have been taken from the 1997 Census of Agriculture.

4.3.5. Farm Worker Exposure Assessment

In calculating LADD, it was assumed that the farm worker would plant approximately 200 acres per day, 3 days per week for 2 weeks each year, for 35 years over a 70-year lifespan. Table 13 lists Mixer/Loader exposure estimates.

Long-term calculations were not performed due to a maximum of 6 days of exposure per year. Short- and intermediate-term calculations (7 days to several months) were performed to assess the worker exposure for the scenario with the highest exposure.

Table 13 - Mixer/Loader Exposure to Dividend™ Treated Seeds

Job Function	Dermal Average Daily Dose (ADD) mg ai/kg bw/day	Inhalation Average Daily Dose (ADD) mg ai/kg bw/day	Short-Term Dermal MOE	Intermediate-Term Dermal MOE	LADD mg ai/kg bw/day	Cancer MOE	Cancer Risk (Q*)
Mixer/Loader	0.000053	0.000014	4.8×10^5	2.4×10^4	0.00000055	8.5×10^6	8.6×10^{-8}

The following equations were used to determine the expected worker exposures to difenoconazole resulting from the opening and loading of bags of canola seed treated with Helix™.

$$\begin{aligned}
 \text{MOE short-term dermal} &= \frac{\text{NOAEL}(25 \text{ MG / KG / DAY})}{\text{ADD}} & \text{MOE intermediate-term dermal} &= \frac{\text{NOAEL}(1.25 \text{ MG / KG / DAY})}{\text{ADD}} \\
 \text{MIXER / LOADER: ADD} &= \left(\left(\text{UNIT EXPOSURE} \left(\frac{\text{MG}}{\text{LB AI}} \right) \right) \times \left(\text{APPLICATION RATE} \left(\frac{\text{LBS AI}}{100 \text{ LBS SEED}} \right) \right) \right) \\
 &\quad \times \left(\frac{\text{LBS SEED}}{\text{ACRE}} \right) \times \left(\frac{\text{ACRES}}{\text{DAY}} \right) \times \left(\frac{1}{\text{BODY WEIGHT (60 kg)}} \right) \times 0.75 \text{ (dermal absorption)} \\
 \text{LADD} &= \text{ADD inhalation \& dermal} \times \left(\frac{\text{Days Worked per Year}}{\text{Total Days per Year}} \right) \times \left(\frac{35 \text{ Years Worked}}{70 \text{ Year Lifetime}} \right) \\
 \text{CANCER RISK} &= Q^* (0.157 \text{ mg / kg / day}) \times \text{LADD}
 \end{aligned}$$

Estimated MOE's for short- and intermediate-term exposures are well above 100, and, therefore below HED's level of concern. Because planting of canola is done mechanically, the mixer/loader scenario represents the highest exposure activity for farm workers. Using the Q_1^* approach, the cancer risk for the mixer/loader was determined to be 8.6×10^{-8} . Since the mixer/loaders are considered to the farm worker group with the highest potential exposures, the cancer risk for farm workers from the proposed seed treatment use of difenoconazole on canola does not exceed HED's level of concern (1×10^{-4}) for non-dietary exposure.

4.3.6. Risk from Post-Application Exposure

There are no post-application exposures expected as a result of the commercial seed treatment use of difenoconazole on canola.

4.3.7. Incident Reports

Incident report data are available for difenoconazole. Two cases have been reported in OPP's Incident Data System by the registrant. They consist of instances of human exposure (in Ohio and Minnesota) which both took place in 1995. Neither case was confirmed and it is not known whether the alleged cases sought medical attention for their symptoms. One report (in which no protective clothing was worn) includes complaints of pain and tingling in the arms and blurred vision. The second report includes complaints primarily of flu-like symptoms and redness of the hands. There were no reports of exposure or illness due to difenoconazole from 1993 to 1996 among 431,684 unintentional cases reported to the nation's poison control centers participating in the Toxic Exposure Surveillance System. The California Pesticide Illness Surveillance Program had no reports of difenoconazole-related illness from 1982 through 1995. Based on lack of incidents from these three sources, no changes in labeling are recommended.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

5.1. Acute Aggregate Risk

The acute aggregate exposure includes dietary (food) and water. Acute risk estimates from aggregate exposure to difenoconazole in food and water are below HED's level of concern. Table 14 summarizes the acute dietary and water exposure.

Table 14 - Acute Scenario (Difenoconazole)

Subgroup ¹	aPAD (mg/kg)	NOAEL (mg/kg)	Food Exposure (from DEEM™) (mg/kg/day)	Water Exposure ² (mg/kg/day)	SCI- GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
Females (13+ years old/ pregnant/nn)	0.25	25	0.000852	0.249	0.00084	0.125	7470
Females (13+ years old/nursing)	0.25	25	0.000889	0.249	0.00084	0.125	7470

Table 14 - Acute Scenario (Difenoconazole)

Subgroup ¹	aPAD (mg/kg)	NOAEL (mg/kg)	Food Exposure (from DEEM™) (mg/kg/day)	Water Exposure ² (mg/kg/day)	SCI- GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
Females (13-29 years old/np/nn)	0.25	25	0.000750	0.249	0.00084	0.125	7480
Females 20+ years old/np/nn)	0.25	25	0.000668	0.249	0.00084	0.125	7480
Females (13-20 years old)	0.25	25	0.000701	0.249	0.00084	0.125	7480

¹ nn= not nursing; np= not pregnant

² Water Exposure(mg/kg/day) = aPAD (mg/kg) - dietary exposure from DEEM™ (mg/kg/day)

From the acute dietary (food only) risk assessments, high-end exposure estimates were calculated for the female 13-50 subgroups only. The % aPADs were below HED's level of concern at the 95th percentile for all female 13-50 years old subgroups with all estimated acute dietary exposures <1% aPAD. The maximum estimated concentrations of difenoconazole in surface and ground water are less than HED's acute DWLOCs for difenoconazole as a contribution to acute aggregate exposure. Therefore, taking into account the uses proposed in this action, HED concludes with reasonable certainty that residues of difenoconazole in drinking water (when considered along with other sources of exposure for which HED has reliable data) would not result in unacceptable levels of acute aggregate human health risk at this time.

5.2. Chronic (non-cancer) Aggregate Risk

There are no registered or proposed residential uses for difenoconazole. Therefore, chronic (non-cancer) aggregate exposure will include risk from food and water only. Chronic (non-cancer) risk estimates from aggregate exposure to difenoconazole in food and water are below HED's level of concern. Table 15 summarizes the chronic (non-cancer) dietary and water exposure.

Table 15 - Chronic (non-cancer) Scenario (Difenoconazole)

Subpopulation	Food Exposure (from DEEM™) mg/kg/day	Water Exposure ¹ (mg/kg/day)	cPAD mg/kg/day	SCI- GROW (ppb)	GENEEC ² (ppb)	DWLOC (ppb)
U.S. Population	0.000005	0.00995	0.01	0.00084	0.016	350
Females (13+ years old/ nursing)	0.000007	0.0100	0.01	0.00084	0.016	300
Non-nursing infants (< 1 yr old)	0.000019	0.00999	0.01	0.00084	0.016	100

¹ Water Exposure(mg/kg/day) = cPAD (mg/kg/day) - dietary exposure from DEEM™ (mg/kg/day)

² According to OPP drinking water guidance (HED SOP 99.5), the 56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment is **0.016 ppb** (0.048 ppm /3).

From the chronic (non-cancer) dietary (food only) risk assessments, the %cPADs were below HED's level of concern (>100%cPAD) for the U.S. population and all population subgroups. The estimated chronic dietary risk associated with the use of difenoconazole is below HED's level of concern. The estimated average concentrations of difenoconazole in surface and ground water are less than HED's chronic (non-cancer) DWLOCs for difenoconazole in drinking water as a contribution to chronic aggregate exposure. HED concludes that there is a reasonable certainty that no harm will result from aggregate chronic exposure to difenoconazole residues.

5.3. Chronic (cancer) Aggregate Risk

There are no registered or proposed residential uses for difenoconazole. Chronic (cancer) aggregate exposure will only include food and water only. Chronic (cancer) risk estimates from aggregate exposure to difenoconazole in food and water are below HED's level of concern. Table 16 summarizes the chronic (non-cancer) dietary and water exposure.

Table 16 - Chronic (cancer) Scenario (Difenoconazole)

Subpopulation	Food Exposure (from DEEM™) mg/kg/day	Water Exposure ¹ (mg/kg/day)	Q ₁ ¹ (mg/kg/day) ¹	SCI- GROW (ppb)	GENEEC ² (ppb)	DWLOC (ppb)
U.S. Population	0.000005	0.00000137	0.157	0.00084	0.016	0.048

¹ Water Exposure(mg/kg/day) = [negligible risk (1x 10⁻⁶) ÷ Q₁¹] - chronic dietary exposure from DEEM™ (mg/kg/day)

² According to OPP drinking water guidance (HED SOP 99.5), the 56-day GENEEC value may be divided by 3 to obtain a value for chronic risk assessment calculations. Therefore, the surface water value for use in the chronic risk assessment is **0.016 ppb** (0.048 ppm /3).

From the chronic (cancer) dietary (food only) risk assessments, the estimated lifetime risk for the U.S. population was 8.6 x 10⁻⁷, which is below HED level of concern (generally 1 x 10⁻⁶). The estimated average concentrations of difenoconazole in surface and ground water are less than HED's DWLOC_{cancer} for difenoconazole in drinking water as a contribution to chronic (cancer) aggregate exposure. HED concludes that there is a reasonable certainty that no harm will result from aggregate chronic (cancer) exposure to difenoconazole residues.

6.0 DATA GAPS

6.1. Chemistry - Revised Section F; PMV

6.2 Toxicology - None

6.3 Occupational Exposure - None

7.0 REFERENCES

All documents are available electronically unless stated otherwise.

DP Barcode(s): D252644
Subject: PP# 9F05045. Difenconazole (Helix™) in/on Canola. Evaluation of Residue Data and Analytical Methods.
From: S. Chun, Chemist
To: Cynthia Giles-Parker/John Bazuin (PM Team 22)
Dated: 10/5/99
MRID(s): 44701701 - 02, 44703527

DP Barcode(s): D203644 and D203645
Subject: PP# 2F04107. Difenconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 5/18/94.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 6/16/94
MRID(s): 43236501 - 03

DP Barcode(s): D210080
Subject: ID# 000100-00740. Difenconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 11/21/94.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 1/18/95
MRID(s): 43467901 - 03

DP Barcode(s): D258772
Subject: PP# 9F05045. Difenconazole (Helix™) in/on Canola. Request for Petition Method Validation (PMV).
From: S. Chun, Chemist
To: Donald A. Marlow, Chief
Dated: 9/3/99
MRID(s): -----

DP Barcode(s): D194842, D199810, D199580, and D195868
Subject: PP# 2F04107. Difenconazole (Dividend) in/on Wheat and Barley. Results of Petition Method Validation for Animal Commodities.
From: G.F. Kramer, Ph.D., Chemist
To: Cynthia Giles-Parker, PM
Dated: 3/30/94
MRID(s): 42818004 - 05

DP Barcode(s): D205118
 Subject: Difenconazole (Dividend) in/on Wheat, and Animal RACs. Amendment of 6/30/94.
 From: G.F. Kramer, Ph.D., Chemist
 To: Cynthia Giles-Parker, PM
 Dated: 7/20/94
 MRID(s): 43292401

DP Barcode(s): D217119, D217120, and D217121
 Subject: ID# 000100-00740. Difenconazole (Dividend) in/on Wheat and Animal RACs. Amendment of 6/29/95.
 From: G.F. Kramer, Ph.D., Chemist
 To: Cynthia Giles-Parker, PM
 Dated: 9/13/95
 MRID(s): 437037-01 thru -02

DP Barcode(s): D253277
 Subject: PP#5E04526 - Difenconazole (CGA-169374 Sico® 259 EC Fungicide) in/on Imported Bananas; and PP#2F4107 - Difenconazole (Dividend®) in/on Wheat and Animal RACs. Calculation of Anticipated Residues.
 From: Susie Chun, Chemist
 To: Dana Vogel, Chemist
 Dated: 3/11/99
 MRID(s): N/A

DP Barcode(s): None
 Subject: Difenconazole - Report of the FQPA Safety Factor Committee.
 From: Brenda Tarplee, Executive Secretary
 To: Melba Morrow, Branch Senior Scientist
 Dated: 10/28/98
 MRID(s): None

DP Barcode(s): None
 Subject: Difenconazole - Report of the Hazard Identification Assessment Review Committee.
 From: Albin Kocialski, Toxicologist and Jess Rowland, Executive Secretary
 To: George Kramer, PhD, Chemist
 Dated: 9/25/98
 MRID(s): None

DP Barcode(s): None
 Subject: Tier 1 FQPA Drinking Water Assessment for Difenconazole
 From: James Hetrick, PhD, Senior Physical Scientist
 To: Cynthia Giles-Parker, PM
 Dated: 2/9/99
 MRID(s): None

DP Barcode(s): D258775
Subject: Difenoconazole - Acute and Chronic (non-cancer and cancer) Dietary Exposure Analyses.
From: Susie Chun, Chemist
To: Susie Chun, Chemist
Dated: 10/12/99
MRID(s): None

DP Barcode(s): D253277
Subject: PP#5E04526 - Difenoconazole (CGA-169374 Sico 259 EC Fungicide) in/on Imported Bananas; and PP#2F4107 - Difenoconazole (Dividend) in/on Wheat and Animal RACs. Calculations of Anticipated Residues. PC Code:128847.
From: Susie Chun, Chemist
To: Dana Vogel, Chemist
Dated: 3/11/99
MRID(s): None

DP Barcode(s): None
Subject: Difenoconazole [Dividend] Quantitative Risk Assessment (Q*) based on Charles River CD-1 mouse chronic dietary study with 3/4's interspecies scaling factor.
From: Lori Brunsman, Statistician
To: Albin Kocialski, Toxicologist
Dated: 12/8/98
MRID(s): None

DP Barcode(s): None
Subject: Carcinogenicity Peer Review of Difenoconazole [Dividend]
From: Jess Rowland, Toxicologist and Esther Rinde, Ph.D
To: Cynthia Giles-Parker, PM
Dated: 7/27/94
MRID(s): None

DP Barcode(s): D189836
Subject: Difenoconazole: Registrant's Response to Deficiencies Cited in Toxicology Review.
From: Jess Rowland, M.S., Acting Section Head
To: Cynthia Giles-Parker, PM
Dated: 9/15/93
MRID(s): 42710010, 42710008, 42710006, 4271005, 42090014 thru 20

(No Accompanying Memo Located)

DP Barcode(s): N/A
Subject: Difenoconazole: 13-week Feeding Study in Rats
From: Ciba-Geigy Corporation
Dated: 1987
MRID(s): 429090022

(No Accompanying Memo Located)

DP Barcode(s): N/A
Subject: Difenoconazole: 28-week Feeding Study in Dogs
From: Ciba-Geigy Corporation
Dated: 1987
MRID(s): 429090012

(No Accompanying Memo Located)

DP Barcode(s): N/A
Subject: Difenoconazole: 13-week Feeding Study in Mice
From: Ciba-Geigy Corporation
Dated: 1987
MRID(s): 429090021

(No Accompanying Memo Located)

DP Barcode(s): N/A
Subject: Difenoconazole: 13-week Feeding Study in Rats
From: Ciba-Geigy Corporation
Dated: 1987
MRID(s): 429090022

(No Accompanying Memo Located)

DP Barcode(s): N/A
Subject: Difenoconazole: 21-day Dermal Study in Rabbits
From: Ciba-Geigy Corporation
Dated: 1987
MRID(s): 429090013

Study: Potential Exposure of Commercial Seed-treating Applicators to the Pesticides
Carboxim-Thiram and Lindane.
Authors: W.E. Grey, D.E. Marthre, S.J. Rogers
Location: Bulletin of Environmental Contamination and Toxicology 31, 244-250.
Dated: 1983

Attachment 1: FQPA Safety Factor Committee Report

Attachment 2: Hazard Identification Assessment Review Committee Report

Attachment 3: Dietary Exposure Analyses

Attachment 4: Codex Form

cc (with attachments): PP# 9F05045, S. Levy (RAB1), A. Kocialski (RAB1)
RDI: Chemists (11/18/99); Team (11/17/99), M. Morrow (11/23/99)
S. Levy: 806T: CM#2: (703) 305-0783; 7509C: RAB1

ATTACHMENT 1 - FQPA Safety Factor Committee Report (*Available Electronically*)

ATTACHMENT 2 - Hazard Identification Assessment Review Committee Report (*Available Electronically*)

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ATTACHMENT 3 - Dietary Exposure Analyses (*Available Electronically*)

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ATTACHMENT 4 - Codex Form